Issued September 16, 1911.

United States Department of Agriculture,

BUREAU OF CHEMISTRY—Circular No. 81.

H. W. WILEY, Chief of Bureau.

THE ACTION OF DRUGS UNDER PATHOLOGICAL CONDITIONS.

BY

WILLIAM SALANT,

Chief, Pharmacological Laboratory, Division of Drugs.

2593°—Cir. 81—11

WASHINGTON : GOVERNMENT PRINTING OFFICE : 1911

CONTENTS.

THE ACTION OF DRUGS UNDER PATHOLOGICAL CONDITIONS.

INTRODUCTION.

The achievements of modern pharmacology may be regarded as twofold in character—scientific, by virtue of its contributions to physiology, and practical, on account of its services to therapeutics. By means of chemical substances we have been able to obtain valuable information concerning the physiological processes in the lower organisms as well as in the higher animals. We have increased our knowledge and broadened our ideas of metabolism in different species of animals, and learned that animals differing widely in structure may yet closely resemble each other physiologically. We have also learned, on the other hand, that important metabolic differences may exist even in forms which are closely allied, and which differ but little, or not at all, in their mode of living and environment.

The most important achievement, however, of modern pharmacology is its contribution to therapeutics. Not only can we lessen or abolish pain by means of chemical substances, but we are now able to eradicate disease. These marvelous practical results are largely due to the study of pharmacological action and chemical constitution, which led to the discovery that the reaction of the cell to a chemical substance may be modified or even completely reversed by a change in one or more elements or radicals of the molecule. The change may consist in the substitution of a group or it may simply be a transposition of a radical in space. The results of these lines of inquiry suggest that pharmacologic action, which is determined by the interaction of cell and chemical substance, ought to vary whichever constant is modified. A change in the cell may be followed, therefore, by a corresponding difference in its reaction to pharmacodynamic agents.

Evidence is accumulating that any disturbance of the complex and delicately adjusted mechanism of the cell may lead to altered chemical and physical activity. Oxidation may be modified if equilibrium between inorganic ions and protoplasm is disturbed. The permeability of the blood corpuscles may be altered by changing the physical condition of the colloids, which is likely to be of interest in connection with the mechanism of the penetration of substances into the cell, whatever that mechanism may be, whether physical, as Overton [58] believes in the case of the basic dyes, or chemical, as is

held by Mathews [45] in regard to these substances and by Koch [34] for strychnin and other drugs.

Indeed, the experimental evidence forthcoming of late years indicates that the reaction of the cell to foreign substances may be quantitatively and even qualitatively different under changed conditions of environment, or after the production of changes morphological, chemical, or physical in character. As will be shown later, a disturbance in any of these factors may bring about corresponding variations in pharmacologic action.

The effects of potassium cyanid on the cell under normal conditions are too well known to need mention. Loeb [38] has shown that the effect on sea-urchin eggs of hypertonic solutions may be inhibited by small quantities of potassium cyanid, and thus save the life of the cell. A complete reversal of the effect of potassium cyanid is thus obtained by simply changing the osmotic conditions of the surrounding fluid of an organism.

According to Warburg,[74] barium chlorid, which has no influence on the respiration of the normal red-blood cells in the bird, inhibits oxygen metabolism after the cell membrane has been destroyed by alternately freezing and thawing.

From Stewart's [67] experiments on the mechanism of hemolysis it appears that the hemolytic action of saponin is diminished when the blood contains ammonium chlorid.

The modifying effect of changes, within as well as without the cell, on the behavior of chemical reagents when brought in contact with it is also made evident by experiments on higher animals and under conditions far more complex. Thus Fleischer and Loeb [19] found that calcium-chlorid solution increased the transudation of fluid into the peritoneal cavity in normal rabbits. According to experiments reported recently by Chiari and Januschke,[11] the pleural exudates caused by various inorganic poisons and diphtheria toxins in dogs and in guinea pigs may be diminished or completely prevented by intravenous injections of small doses of a 3 per cent solution of calcium chlorid.

The work of Ellinger [15] shows that a change of chemical reaction in the surrounding fluid may render innocuous the poisonous action of cantharidin on the glomeruli of the kidney. Cantharidin when given to rabbits which were fed carrots, thus rendering the urine intensely alkaline, was not followed by nephritis.

Ehrlich [16] observed, in rabbits infused with a solution of methylene blue, well marked staining of the pancreas due to staining of the granules and protoplasm of the islands of Langerhans. He did not observe any staining of the nerve ends under these conditions. If certain dyes of the triphenylmethane series be added to the solution of methylene blue, the nerve ends become stained, although neither of

the substances alone is capable of staining these end organs. Ehrlich [16] assumed, therefore, a change in the function of the nerve apparatus, which alters its absorbing power. The studies of Bondy and Jacoby [6] on the distribution of salicylic acid have shown that the joints of animals infected with *Staphylococcus aureus* contain larger quantities of this substance than those of normal animals similarly treated. The distribution of iodin in the tissues after the administration of potassium iodid shows that in health the blood contains more iodin than any other tissue. According to the findings of Loeb and Michaud,[39] the eye and the lungs of tuberculous animals may contain more iodin than the blood, while the organs with tubercular lesions contained from 50 to 150 per cent more iodin than the same organs when free from this disease. They also state that the amounts of iodin were proportional to the extent of the involvement, and varied with the progress of the tuberculous process. Differences in the distribution of iodin after the administration of potassium iodid have also been reported in carcinoma by Von den Velden.[70]

These facts indicate that the selective action of drugs is at least quantitatively modified by morbid changes.

That interference with the functions of an organ or its complete removal from the body modifies the action of drugs was pointed out long ago by the classical experiment of Claude Bernard [3] and later by Hermann [25] both of whom showed that after ligation of the ureter, curara becomes toxic when given by mouth.

The investigations on the pharmacology of adrenalin have shown that under conditions induced experimentally some of its characteristic actions observed in normal animals may be either suppressed or completely reversed. Ellinger [15] failed to observe adrenalin glycosuria in rabbits when nephritis had been produced by cantharidin or by ligating the renal blood vessels. Meltzer [47] states that after cutting the vaso-motors on one side, or by eliminating the central innervation of the blood vessels in the ear of the rabbit, the subcutaneous administration of medium doses of adrenalin was followed by constriction, while in the normal rabbit the drug causes dilatation of these vessels. The action of adrenalin varies also in inflammatory conditions, according to the same observer [48]; for he failed to obtain in inflamed areas the constriction of the vessels which it causes in simple hyperemia.

ORGANS OF INTERNAL SECRETION.

Within recent years data have been accumulating on the behavior of drugs in conditions of profound disturbance of metabolism such as is caused by the removal of the organs of internal secretion. Omi's [56] experiments with salicin in the dog after removal of the pancreas brought to light the interesting fact that the liver of such

animals acquires the ability to break up this glucosid into its component parts—a function the livers of normal carnivora possess, to a slight degree or not at all, while Jeandelize and Perrin [30] claim to have observed an increase in the toxicity of sodium arsenate and of mercuric chlorid in thyroidectomized rabbits.

On the other hand it has been the experience of many clinicians that patients with exophthalmic goitre are very susceptible to anesthesia. After feeding thyroid to mice and guinea pigs Hunt and Seidell [29] observed diminished resistance to morphin. They also reported that thyroid feeding lowered the resistance of rats to acetonitrile, but increased the resistance of mice to this substance.

FEBRILE CONDITIONS.

The complex physical and chemical processes set in motion by febrile conditions have within recent years claimed the attention of the physiologist as well as that of the biochemist. The data already obtained, meager as they are, justify the hope that this is a fruitful line of investigation, and that patient and diligent efforts will have their reward. We know already that protein katabolism is much accelerated in fever. According to Kastle [33] oxidation in many diseases, accompanied by a febrile condition, shows many departures from the normal. As this is probably true of other processes in the body under these conditions, it would seem a priori that the reaction to foreign substances introduced into the body would also be altered. Indeed, this contention is fully borne out by experiments on animals as well as by bedside experience, as shown by the results obtained with the antipyretics.

Wachsmuth [73], and later Liebermeister [37], announced about half a century ago that the action of quinin is different in health and in disease. Liebermeister made numerous observations with this drug under a variety of conditions, accompanied by pyrexia, and noticed that in some cases of typhoid, doses which exert a marked depression of temperature in the later stages of the disease, have no antipyretic effect in its earlier stages. It then occurred to him to study the action of the drug in health as regards its effect on temperature. He, therefore, made a number of observations on quinin in the case of convalescents from typhoid and other febrile diseases when the temperature became normal. The results he obtained show that in some cases a marked reduction of temperature occurred after the administration of the same doses of this drug. Again no effect on the temperature was observed, but even in those cases of apyrexia in which quinin reduced body temperature, the effect was less marked than in fever. The administration of the drug in health, as observed by Liebermeister, in one case shows that large doses may be borne with-

out affecting body temperature. Thus 40 grains of quinin administered in seven hours failed to lower the temperature in a healthy subject. Likewise, Jurgensen [32] stated that doses which lower the temperature in disease remain without effect in health. Buss [9], who experimented with doses of 1 to 2 grams, found that these amounts do not affect temperature in health.

Observations on the synthetic antipyretics are not quite so concordant. Riess [60] failed to obtain a marked reduction of temperature with salicylic acid in health. After the administration of 5 grams of this drug he observed a fall of only 0.9° C., while the same dose when given under febrile conditions lowered the temperature 2° to 6° C. Buss [8] (who carried out experiments on himself) and others claimed that they never observed any lowering of temperature in febrile cases. Kairin in doses up to 1.5 grams, according to Filehne,[18] has no effect in health; single doses of 0.5 to 1 gram lower the body temperature 0.5° to 2° C. in fever. According to Cohn and Zadek [13] this drug does not affect normal temperature after the administration of 3 grams. When given in pneumonia, typhoid and in other febrile conditions, 0.25 gram lowered the temperature 0.5° to 1° C. Maragliano and Queirolla [44] gave 4 to 5 grams an hour to 10 healthy individuals, but were not able to induce a lowering of the temperature in any of them; 0.5 to 1 gram doses of kairin given in fever reduced the temperature 2° to 4°. Furthermore, the antipyretic effect noticed by these investigators varied directly with the fever. Murri [54] observed a fall of 3° to 5° in febrile patients, but obtained no effect in normal individuals when he gave them the same amounts distributed over an equal length of time. Similar results were obtained with antipyrin. Some observers state that a slight reduction of temperature was noticed after taking antipyrin in a febrile condition, but reduction was much less than in disease accompanied by fever. Friedrich Müller [53] observed that after the administration of large doses of antipyrin the temperature goes down, even in normal individuals, but the reduction is slight, only 0.2°. The same observer reported marked diminution of the elimination of nitrogen when antipyrin was given in fever, but observed little or no effect on protein metabolism in health when the drug was administered.

Pusinelli [59] corroborated the observation of Müller on the effect of this drug on temperature in health. After the administration of 1 gram to a healthy individual the reduction in temperature amounted to a few tenths of a degree Celsius; but Pusinelli, on the contrary, observed a slight rise of temperature after giving doses of from 2 to 3 grams to a healthy individual. The dose he employed in fever (which varied between 0.5 and 2 grams) lowered the body temperature 1° to 2° Celsius one hour after its administration; later a further

decrease was noted. Acetanilid, as might be expected, has been the subject of numerous experimental studies on man and animals as regards its action on the body temperature. Simpson[66] reported a slight fall of temperature (about 0.6° F. maximum) after taking fairly large doses in health. The same doses in febrile conditions were followed by a fall of 2° F. Cahn and Hepp,[10] who made observations on animals with relatively large doses, stated that the temperature of normal animals is not affected. This is apparently contradicted by the experiments of Lépine[36] and Bokai.[5] A critical examination, however, of their experiments shows that the conditions under which they were carried out leave serious doubt as to whether the animals could be considered normal. Bokai experimented on dogs in a condition of narcosis induced by opium and gave them 0.25 gram of acetanilid per kilo, which is a very large dose.

The size of the dose may also account for the results obtained by Lépine, who administered 0.3 gram of acetanilid per kilo intravenously to dogs and subcutaneously to rabbits. Sackur,[63] who carried out an elaborate series of experiments on 48 individuals with sodium salicylate, kairin, antipyrin, thallin, acetanilid, and phenacetin, came to the conclusion as a result of his observations that doses which lower the temperature in disease have practically no influence on temperature in health. Indeed, in some cases he observed a rise of temperature in healthy people after the administration of these drugs.

VARIATIONS IN BODY TEMPERATURES EXPERIMENTALLY INDUCED.

The difference in response of the body to these drugs in febrile conditions may be due, however, to toxins as well as to the uneven rise of body temperature. Inanition, partial or complete, is another factor which ought to be taken into account, since little or no food is taken in these conditions. Let us examine what evidence we have on these points under conditions in which the body temperature was varied by experiments on healthy animals, causing it either to rise above or sink below the normal.

Wagner[a] has shown that the immunity of the hen to anthrax may be abolished by producing a hypothermia. Gibier and Metschonikoff[a] increased the susceptibility of the frog to this disease by submerging it in water at a temperature of 35° to 37° C. Similar results were reported by Doyen and Courmont,[14] and later by Morgenroth,[52] who abolished the immunity of the frog to tetanus toxin by raising the surrounding temperature to 20° C.

The influence of temperature on the toxicity of inorganic substances, alkaloids, glucosids, and narcotic drugs has been the subject

[a] Quoted by Zeehuisen.

of a number of investigations. The narcotic effect of morphin on frogs is said to be increased, according to Hausmann,[22] when these animals are placed in water at a temperature of 20° to 26° C. He pointed out that the narcotic effect of this drug is decreased when the temperature is lowered, but that tetanus occurs more readily.

This investigator[23] also made very interesting observations in his studies with colchicin, tannin, saponin, and abrin on hibernating bats. He found that the toxicity of these substances is much greater when treated animals are placed in a thermostat than when allowed to remain in the cold. The experiments he carried out later with Kolmer[24] on unicellular animals corroborate these findings. Colloidal silver was shown to be more toxic to paramacia when the temperature of the solution was raised from 15° C. to 33° C. Their results with colchicum in this connection were specially striking. Paramacia placed in 1 per cent solutions were normal after four days, when the temperature was 15° C., but when the temperature was raised to 33° C. the duration of life was only three and one-half hours.

Zeehuisen[76] studied the action of apomorphin and of morphin on pigeons in hypothermia and in hyperthermia. When the temperature was moderately lowered he observed diminished movements and a decreased tendency to vomiting, after the administration of apomorphin. When the temperatures of the pigeons were reduced 3° to 15° C., there was complete inhibition of emesis. The toxicity was at the same time increased; there was greater nervous irritability and convulsions were induced more easily. When the temperature was higher than normal the emetic action of the drug was lost and the movements of the beak ceased. The toxicity of morphin was increased when the temperature was raised, but was not affected in hypothermia.

According to Veley and Waller,[69] who studied the effect of chloroform, alcohol, quinin, and aconitin, the toxicity was greater at a higher temperature. In their observations on the effects of these substances on the contraction of striated muscle, they found that a muscle exposed to a two-thousandth normal solution of quinin recovers at once at a temperature of 19° C.; when the temperature of the solution is 25° C., recovery is delayed five minutes. Muscular fatigue after alcohol is similarly influenced. Recovery begins after one minute at a temperature of 20° C., but is retarded four minutes at a temperature of 24° C.

STARVATION OR A RESTRICTED DIET.

Experiments with alanin on man and animals in a state of starvation are suggestive from our point of view. After the feeding or the subcutaneous injection of 15 grams of inactive alanin in the case of starving dogs Rahel Hirsch[26] found the *l*-alanin in the urine.

The same amount, she states, was completely destroyed when given to well-fed dogs. She reported similar results with alanin in starving phloridzinized dogs, and Brugsch and Hirsch [7] corroborated these findings in a professional faster.

These experiments would lead to the expectation that a difference may also result in the action of drugs when the diet has been restricted or when food has altogether been withheld for a sufficient length of time. The following investigations lend support to this view:

Jordan,[31] who carried out a number of experiments with digitalin on dogs which he allowed to fast from three to twelve days, reported that symptoms appeared after much smaller doses of the drug in starvation. It is interesting to notice that he also observed diminished irritability of the vagus in hunger, which decreased with the length of starvation. According to Roger,[61] atropin and quinin sulphate were less toxic to rabbits starved from twenty-four to twenty-six hours. He found that after injection of quinin sulphate into a peripheral vein the minimum toxic dose was about 25 per cent greater in starving rabbits, but when this drug was injected into the portal vein the fatal dose for the well-fed rabbits was 160 mg per kilo and only 86 mg per kilo for the starving animals. He obtained the same results with atropin, but his findings with nicotin were negative.

Aducco [1] studied, in several species of animals, the resistance of drugs in starvation and found that in inanition strychnin, phenol, and cocain are more poisonous to dogs, rabbits, guinea pigs, and pigeons.

Monaco and Trambusti,[51] on the other hand, reported that death in phosphorus poisoning is delayed in complete inanition, while an abundant diet hastened death in dogs and rabbits poisoned with this substance. The work of Mansfield [42] shows that doses large enough to cause a slight reaction in well-nourished rabbits were fatal to the same animals when starved for five to ten days. According to Mansfield and Fejes,[43] the brain in starving rabbits retains larger amounts of chloral than the brain of well-fed rabbits. At the end of thirty minutes the amount of chloral in the brain was about the same in normal and in starving rabbits. At the end of one hour the difference was about 50 per cent. After one and one-half hours the brain of the starving rabbit contained almost twice as much chloral as that of the normal rabbits. The experiments with alcohol failed to show, however, any difference in the alcohol content of the brains of well-fed and of starving rabbits.

In experiments on the toxicity of caffein, Salant and Rieger [65] found that rabbits which had been starved for five or six days were less resistant to this drug than well-nourished rabbits. The toxicity

when food was withheld increased 30 per cent in nearly all the cases examined. On the other hand, the recent work of Hunt [28] shows that partial starvation may increase the resistance of animals to some poisons. He found that mice and guinea pigs which received only small quantities of food survived doses of acetonitrile which proved fatal to these animals when the amount of food given was unrestricted.

CHRONIC ALCOHOLISM.

Attention may also be directed toward chronic alcoholism and chronic lead poisoning as conspicuous examples in which changes in the body associated with abnormal metabolism determine important differences in the behavior of drugs, both as to their total effect or as to some of the changes they undergo in the body.

Hunt [27] has shown that resistance to acetonitrile in chronic alcoholism is diminished. In experiments made recently by the writer [64] with chenopodium oil it was observed that the toxicity of this substance is markedly diminished in rabbits which have received alcohol for several weeks. Some unpublished work of this laboratory with caffein and theobromin indicates that demethylation was retarded in rabbits which received alcohol for two weeks. Since demethylation is very probably an attempt of the body to reduce the toxicity of the methyl purins, it may be inferred that retarded demethylation is likely to increase the toxicity of the substances. In numerous observations made by the writer on the toxicity of caffein in animals there was a marked increase in the susceptibility of rabbits to caffein when these animals showed well-marked lesions of coccidiosis of the liver, or other lesions. It is quite possible that retarded demethylation is responsible for these results.

As far as could be determined no experiments on resistance to drugs in chronic lead poisoning have been made. The statement of Otto Loewi,[40] to the effect that much smaller doses of atropin are effective in this condition, was the only reference to the subject found in the literature.

FATIGUE.

The subject of fatigue has received considerable attention within recent years from physiologists in this country and abroad. The work of Lee [35] on frog muscle indicates that muscular fatigue in these animals is caused by carbonic acid, sarcolactic acid, and the monobasic phosphates. Whether other substances may likewise cause fatigue, as has been asserted by some investigators, is for the present unknown, nor are there any data regarding the causation of general fatigue of the nervous system. Evidence of the presence of profound changes of the nervous system in this condition was given by the recent work of Barbour and Abel.[2] In their experiments with acid

fuchsin, they made the following observations. Tetanus appeared in normal frogs in from 1 to 24 hours after the injection of 1 to 4 mg of acid fuchsin per kilo, while in some frogs even much larger doses failed to produce symptoms. Frogs which had been exercised until fatigue was produced reacted to this drug much more quickly, and after smaller doses. Some of these experiments were carried out on animals in normal condition and again several days later on the same animals when a state of fatigue was induced; doses of the drug, which showed no effect on these animals at first, were followed by tetanus within 10 minutes after injection when they were fatigued.

CIRCULATORY ORGANS.

Abnormalities of the organs of circulation, whether produced experimentally or occurring naturally, likewise afford instances of modified pharmacologic action which may be quantitative or even qualitative. Von Plavec [71] and others pointed out several years ago that cardiac activity is increased in the diseased heart after theobromin, but the drug has no effect on the heart in health. Caffein in collapse is cited by this author as another instance. A dose just large enough to cause a mild stimulating effect in the healthy individual will increase many times the pulse volume and amplitude in collapse.

The same observer [72] reported that from 0.2 to 0.3 gram of theobromin or theophyllin given three times a day have no effect on the frequency or quality of the pulse in health. In advanced cases of failing compensation, however, he noticed a striking increase of cardiac activity after the administration of such doses of these drugs. Frankel and Schwarz [21] made a number of experiments with milligram doses of strophantin, which they injected intravenously into individuals with normal heart action, but failed to notice any circulatory changes or any effect on diuresis. The same doses of strophantin, when given in cases of valvular disease with failure of compensation well established, were followed by a decrease of frequency and an increase in amplitude of the pulse. Cloetta's [12] studies with digitalis are of interest in this connection. He has shown that in rabbits in which he induced aortic insufficiency with cardiac hypertrophy, digitalis caused diminished cardiac hypertrophy and changes in the circulation. Similar experiments with digitalis on the healthy rabbit were without any effect.

According to Bielfeldt,[4] the injection of glycogen in healthy horses is followed by slight rise of temperature and increased frequency of pulse and respiration. In sick horses which suffer from cardiac weakness, the injection of glycogen decreases pulse frequency and at the same time strengthens heart action. Eychmüller [17] made a number of

observations with therapeutic doses of digalen. He reported a moderate increase in amplitude and slowing of the heart beat in the healthy heart. In valvular lesions with failing compensation the effect of the drug was much more marked in these respects. That differences in the mechanism of adjustment in abnormal conditions are in some instances at least the cause of altered pharmacologic action is strikingly illustrated in the case of amyl nitrite. According to Rzentkowski,[62] this drug does not cause a fall of blood pressure in health as it does in cases of arterio-sclerosis. This he believes is because in health there is a compensatory constriction of the abdominal vessels which is lost in arterio-sclerosis.

Injury to the cardiac muscle likewise modifies its reaction to drugs. This was shown some years ago by Talma and Weyde,[68] who reported that the action of ammonia was much less favorable on the heart of the frog after it was poisoned by quinin. More recently Nicola [55] studied the influence of barium chlorid in fatty degeneration of the heart induced experimentally. He states that barium chlorid has no effect on cardiac activity when the process is well advanced. According to the observations which Wiggers [75] reported recently, anæmia produced experimentally modifies the action of a number of drugs. Retardation of the pulse observed after the administration of adrenalin under normal conditions was not seen when this drug was given in hemorrhage, according to this observer. Digitalis likewise loses its retarding effect under these conditions. Changes in the action of the nitrites, nitroglycerin, ergotin, morphin, and chloroform on the circulation as a result of hemorrhage have also been reported by this author.

GENERAL DISCUSSION.

These data, although incomplete, ought to be sufficient to serve as a stimulus to further research in the direction suggested. To assume that a substance introduced into the body will produce the same effect under all conditions is unjustifiable and may lead to error and in therapeutics to serious consequences. The factors which determine the action of a drug are numerous. Mention has been made of the fact that oxidation, synthesis, and other chemical processes in the body are in all probability affected in disease. In addition to these the processes of absorption and elimination should be taken into account. It has been shown experimentally that these processes are modified under some conditions. Thus, after the removal of the kidneys in the rabbit, the rate of absorption from the peritoneal cavity is increased. This was shown several years ago by Meltzer and Salant,[50] and has been corroborated recently by Fleischer and Loeb.[20] Mayerhofer and Pribram [46] observed improved absorption of toxins,

ferments, potassium chlorid, proteins, and so on from the small intestine of animals in which enteritis was induced experimentally. Outikhine's [57] observations in experimental keratitis afford corroborative data on this subject. He states that the coefficient of absorption of fluorescin is increased from 2 to 38.4 in the anterior chamber of the eye and atropin is absorbed much faster from the conjunctiva in experimental keratitis. The recent experiments of McCrudden,[41] on the other hand, point to increased rate of elimination when the intestines are hyperemic or inflamed. He found that the elimination of morphin is more rapid after the administration of croton oil, quillaja, senaga, mustard oil, or alcohol. McCrudden [41] believes that since these substances are local irritants they would cause hyperemia and increased secretion, which favors better elimination of this drug.

It would seem, therefore, that under some conditions the drugs may be more easily absorbed and eliminated faster. On the other hand, if the organs of absorption and elimination are diseased so that their functions are not affected to the same degree, and compensation is not established, the effect of a poison might, under these conditions, be different. As all the processes called into existence by experimental procedure, or in the course of disease, are far from being understood, predictions as to the action of a drug can at best be only approximate; and, indeed, sometimes the results may be altogether surprising. The following illustration is drawn from an experience of the author several years ago when engaged in a series of studies on the effect of strychnin in nephrectomized rabbits.[49] Since strychnin is eliminated by the kidneys only, their excision ought to render the drug more toxic to this animal. Indeed, it was taken for granted by some experimenters that strychnin administered to nephrectomized animals would necessarily produce the usual symptoms as soon as enough of it had been administered, even if given in divided doses. As a matter of fact, the single toxic or fatal dose was found in these experiments to be even somewhat larger after the kidneys were removed. More interesting still was the fact that when the drug was injected very slowly, or by the administration of subminimum doses at sufficiently long intervals of time, from three to four times the amount was required to produce the characteristic reaction.

This is certainly a striking illustration of how misleading a priori conclusions in biology may be. The value of speculation and of theory is by no means to be underrated. Indeed, this is to be encouraged in every laboratory for biological experimentation. Its greatest and, indeed, its only value, however, is to stimulate investigation, for experimental evidence is the only safe and reliable test of the validity of a theory.

BIBLIOGRAPHY.

1. Aducco. Centrbl. Inn. Med., 1894, **15** : 700.

2. Barbour and Abel. J. Pharm. Exper. Ther., 1910, **2** : 167.
3. Bernard, Claude. Rev. Cours Scientifique, 1865, **2** : 179.
4. Bielfeldt. Diss. Bern., 1909.
5. Bokai. Deut. Med. Wochnschr., 1887, **13** : 905.
6. Bondy and Jacoby. Hofmeister's Beitrage, 1906, **7** : 514.
7. Brugsch and Hirsch. Zts. Exper. Path. Ther., 1901, **3** : 638; 1907, **4** : 947.
8. Buss. Deut. Arch. Klin. Med., 1875, **15** : 457.
9. ———. Ueber Wesen und Behandlung des Fiebers, Stuttgart, 1878, p. 168.

10. Cahn and Hepp. Centrbl. Klin. Med., 1886, **7** : 562.
11. Chiari and Januschke. Arch. Exper. Path. Pharm. 1911, **65** : 120.
12. Cloetta. Arch. Exper. Path. Pharm., 1908, **59** : 209.
13. Cohn and Zadek. Deut. Med. Wochnschr., 1883, **9** : 487.

14. Doyen and Courmont. Compt. rend. Soc. Biol., 1893, **45** : 618.

15. Ellinger. Münch. Med. Wochnschr., 1905, **52** : 499.
16. Ehrlich. Studies on Immunity, tr. by Bolduan, 1906.
17. Eychmüller. Berl. Klin. Wochnschr., 1909, **46** : 1677.

18. Filehne. Berl. Klin. Wochnschr., 1882, **19** : 681.
19. Fleischer and Loeb. J. Exper. Med., 1910, **12** : 288.
20. ——— ———. 1910, **12** : 487.
21. Frankel and Schwarz. Arch. Exper. Path. Pharm., 1908, suppl., p. 188.

22. Hausmann. Arch. Exper. Path. Pharm., 1905, **52** : 315.
23. ———. Arch. Ges. Physiol., 1906, **113** : 317.
24. ——— and Kolmer. Biochem. Zts., 1907, **3** : 503.
25. Hermann. Arch. anat. Physiol. Wiss. Med., 1867, p. 64.
26. Hirsch. Zts. Exper. Path. Ther., 1905, **1** : 141; 1906, **2** : 668.
27. Hunt. U. S. Public Health and Marine-Hospital Service. Hyg. Lab. Bul. 33.
28. ———. Ibid., Bul. 69.
29. ——— and Seidell. Ibid., Bul. 47.

30. Jeandelize and Perrin. Compt. rend. Soc. Biol., 1908, **1** : 233; 235; 1910, **68** : 146.
31. Jordan. Centrbl. Med. Wiss., 1895, **23** : 145.
32. Jurgensen. Die Korperwarme des Gesunden Menschen, Leipzig, 1873, p. 41.

33. Kastle. U. S. Public Health and Marine-Hospital Service. Hyg. Lab. Bul. 31.
34. Koch. J. Pharm. Exper. Ther., 1910, **2** : 265.

35. Lee. J. Amer. Med. Assn., 1906, **46** : 1491.
36. Lépine. Lyon. Med., 1886, **53** : 269.
37. Liebermeister. Deut. Arch. Klin. Med., 1867, **3** : 600.
38. Loeb. Die Chemische Entwickelungs Erregungen des Tierischen Eies, 1909, p. 53.
39. ——— and Michaud. Biochem. Zts., 1907, **3** : 307.
40. Loewi. Wien Klin. Wochnschr., 1910, **23** : 274.

41. McCrudden. Arch. Exper. Path. Pharm., 1910, **62** : 374.
42. Mansfield. Arch. Int. Pharm. Ther., 1905, **15** : 467.
43. ——— and Fejes. Arch. Int. Pharm. Ther., 1907, **17** : 348.
44. Maragliano and Queirolla. Centrbl. Med. Wiss., 1884, **22** : 672.
45. Mathews. J. Pharm. Exper. Ther., 1910, **2** : 167.
46. Mayerhofer and Pribram. Zts. Exper. Ther., 1909, **7** : 247.
47. Meltzer and Meltzer. Amer. J. Physiol., 1903, **9** : 252.
48. ———. J. Med. Res., 1903, **10** : 136.
49. Meltzer and Salant. J. Exper. Med., 1901, **5** : 643.
50. ———. J. Med. Res., 1903, **11** : 30.
51. Monaco and Trambusti. Centrbl. Inn. Med., 1894, **15** : 701.
52. Morgenroth. Arch. Int. Pharm. Therap., 1900, **7** : 265.
53. Müller. Centrbl. Klin. Med., 1884, **5** : 570.
54. Murri. Centrbl. Med. Wiss., 1884, **22** : 428.

55. Nicola. Arch. Farm. Sper., 1908, **7** : 219.

56. Omi. Biochem. Zts., 1908, **10** : 258.
57. Outikhine. Diss. St. Petersburg, 1907; Ann. Ocul., 1909. **141** : 74.
58. Overton. Vierteljahrs. Naturforsch. Ges. Zurich, 1899. **44** : 88.

59. Pusinelli. Deut. Med. Wochnschr., 1885, **11** : 145.

60. Riess. Berl. Klin. Wochnschr., 1875. **12** : 673.
61. Roger. Compt. rend. Soc. Biol., 1887, ser. 8, **4** : 166.
62. Rzentkowski. Zts. Klin. Med., 1909, **68** : 3.

63. Sackur. Diss. Breslau., 1890, p. 35.
64. Salant. Proc. Amer. Soc. Pharm. Exper. Ther., J. Pharm. Exper. Ther., 1911, **2** : 391.
65. ——— and Rieger. Proc. Amer. Soc. Pharm. Exper. Ther., J. Pharm. Exper. Ther., 1910, **1** : 569.
66. Simpson. N. Y. Med. Rec., 1887, **32** : 706.
67. Stewart. J. Pharm. Exper. Ther., 1909, **1** : 49.

68. Talma and Weyde. Zts. Klin. Med., 1885, **9** : 276.

69. Veley and Waller. Proc. Roy. Soc. Lond., 1910, ser. B, **82** : 205.
70. Von Den Velden. Biochem. Zts., 1908, **9** : 54.
71. Von Plavec. Arch. Int. Pharm. Ther., 1904, **13** : 275.
72. ———. Ibid., 1908, **18** : 499.

73. Wachsmuth. Arch. Heilkunde, 1863, **4** : 73.
74. Warburg. Zts. Physiol. Chem., 1911, **70** : 413.
75. Wiggers. Proc. Amer. Soc. Pharm. Exper. Ther., J. Exper. Pharm. Ther., 1911, **2** : 391.

76. Zeehuisen. Arch. Exper. Path. Pharm., 1895, **35** : 181.